REMARKS

Status of the Claims

Claims 1, 2, 4-13 and 15-20 are pending in the application. Claims 1, 8 and 11 have been amended herein for clarity. Claims 12 and 13 are withdrawn, and claim 14 has been cancelled. No new matter has been added by way of the amendments. Entry and consideration thereof are respectfully requested.

Claim Objections

Claim 8 has been objected for a misspelling in the word "barrier." Claim 8 has been amended to correct this error. Withdrawal of the objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, 2nd Paragraph

Claims 1-2, 4-11, and 14-20 have been rejected under 35 U.S.C. § 112, 2nd paragraph as being unclear. More specifically, claim 1 has been rejected as being unclear with regard to whether carbopol is a required limitation. Claim 1 has been amended for clarity by deleting the recitation of "carbopol."

Claim 1 has been further rejected with the assertion that it is not clear whether the carboxypolymethylene is both a thickening agent and an emulsifier. Claim 1 has been amended to clarify that the thickening agent and emulsifier are separate components.

Finally, the Examiner asserts that it is unclear whether the instant invention is, in fact, a composition, or a multi-component assembly of the recited components, which are not actually mixed together, i.e. a "kit." As described in the specification, the instant invention is a composition. However, the various components of the composition are separately prepared and then mixed together. Claim 1 has been amended to clarify the feature of the invention.

As the above amendments address and overcome the rejections and clarify the metes and bounds of the claims, withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1-2, 4-10 and 14-20 have been rejected under 35 U.S.C. § 103 as being unpatentable over Klein (US '918), in view of Parrilla (US '838) and Beitner (US '171). Claim 11 has been rejected over the aforementioned references and additionally Chen (US '182).

Klein is relied on for teaching topical compositions that contain all of the components of the instant invention, except the anesthetic agent and proteolytic compound. Parrilla and Beitner are respectively relied upon for teaching the treatment of burns with compositions that contain proteolytic enzymes, such as papain, and the treatment of burns with an anesthetic. The Examiner asserts that it would be obvious to include the proteolytic enzyme of Parrilla and anesthetic of Beitner in the composition of Klein, since these additional agents are being used for the same purpose as in the prior art. Chen is additionally relied upon for teaching the use of chlorhexidine in burn treatment compositions. Applicants traverse these rejections and withdrawal thereof is respectfully requested.

Background

After skin tissue has sustained an injury or been burned, cell death ensues, chemical substances are released that stimulate pain-transmitting nerves, there is a loss of continuity of the skin with exposure of underlying elements, and if the injury or burn remains exposed, it may become colonized by bacteria. A series of similar events is initiated by the body for abrasions, superficial burns and wounds. This process is known as biological wound repair and consists of a cascade of events referred to as tissue repair phases.

The first response of the body to injury is acute inflammation, which has three purposes:

- debridement of necrotic tissues,
- phagocytosis (removal) of bacteria, and
- a first immunological response (defense).

Inflammation is promoted by ischemia, the presence of necrotic material, bacteria, nerve endings exposed to the environment, and may be decreased by wound care with non-traumatic techniques, hemostasia, appropriate asepsis, and by avoiding mistreatment of the tissues. See for example, *Cirugía Plástica, Reconstructiva y Estética*, 3rd ed., Coiffman Vol. 1, Chapter 29, Erikas Liliana Kurzer, pages 266-277.

All living beings isolate themselves from the environment with a layer of cells that form a protecting and water-tight envelope called the epithelium. When the epithelium is injured, it must regenerate itself very rapidly to reestablish its continuity. In order to cover a raw surface, the epithelium must grow and migrate, with migration being the most important phenomenon. It has been known that the epithelium does not migrate over dead or necrotic tissues; rather it migrates underneath the edge of the wound and spreads along the underlying healthy tissues. The presence of debris and of necrotic tissue mechanically interferes with the epithelializatoin process, thus it is very important to remove them from the wound area. *Simposio de ciencias básicas in cirugía plástica,* The C.V. Mosby Company (1976), Vol. 15, Chapter 11, pages 87-89.

Infection is the most feared complication in skin burns or injuries and there are several factors that may promote infection:

- burns cause the loss of the main defense barrier of the body, i.e. the skin
- the eschar or crust that follows the injury does not provide any protection against bacterial colonization (need of a protecting barrier)
- the accumulation of proteins in the wound, tissue hypoxia and ischemia all contribute to the development of locales infection *Cirugía Plástica, Reconstructiva y Estética*, 3rd ed., Coiffman, Vol. 1, Chapter 4, Linda Guerrero.

In addition, a study conducted by Burke showed that 65% of infected burns were caused by air-borne cross contamination. Burke, *The Contribution of bacterial isolated environment to the prevention of infection in seriously burned patients,* Ann. Surgery, 186: 377-387, 1997.

The International Society for Burn Injuries suggested three consideration for infections:

- Source of infection: either endogenous from the patient's own flora, or exogenous from the environment. Seventy per cent of all burns are invaded by gram-positive bacteria during the first few days, and from the 5th day on 55% are invaded by gram-negative germs.

- Transmission: Either through direct contact, or microorganisms in the environment

- Patient's Susceptibility: The loss of skin and mucous membranes, stress caused by pain, eschars, etc.

Alternatively the following considerations offer an optimal chance of burn healing, Artz C, Moncrief J, *"Burns"* W.B. Saunders Company (1979), Chapter 13, pages 195-211.

1- Containment and control of potentially infecting bacteria

2- Prompt removal of debris and unviable tissues

3- Prevention of accumulation of secretions in the burn

4- Isolation of the wound from contamination sources

5- Creating an ideal and suitable environment for wound healing

6- Preventing wound dehydration due to excessive water evaporation

7- Maintaining the burned area in a resting state

8- Take all the appropriate measures to increase wound healing.

At the *12th Annual Meeting of the European Association of Wound Management* held in Granada, Spain, May 23-25/2002, it was concluded that: "Preventing mistreatment or trauma (intervention) to the wounds and pain to the patient were considered as the most relevant elements concerning the care of a skin injury. Removing dressings causes great pain; thus, a non-traumatic and painless dressing is a highly desired feature."

Pain is defined as an unpleasant sensorial and emotional experience associated with actual or potential tissue damage (Fields HL, 1998; Cohen VL, 1998). The importance of pain is such, that in addition to its causing anguish to the sufferer, it can also induce bodily reactions that may be life-threatening. Therefore, today there is the trend to consider pain as the fifth vital that should be considered by all health-care professionals. The true importance of pain management consists of creating optimal conditions for wound healing. Pain plays a protective role in nature by preventing damage; however, postoperative pain may also be destructive because it increases cell stress, as well as autonomic, somatic, and endocrine responses. *Worldwidewounds.com/2001/march/pediani/pain-relief-surgical-wounds-html#* Johnson, Goodwin, Kehlet

The concept of applying barrier hydrogel, i.e. hydrocolloid gels barriers that provide the necessary environment to promote tissue repair, using no antibiotics in infection-free patients goes back to 1997, and were termed "non-traumatic gel dressings" (Thomas S, Loveless P., *A comparative study of the properties of twelve hydrocolloid dressings*, World Wide Wounds, July 1997).

The instant invention

Based on above discussed issues concerned with wound complications and healing, the instant invention has been designed for the topical treatment of skin injuries. Thus, the goals of the invention are:

- to prepare the wound bed by creating an optimal environment for fast tissue regeneration;
- to isolate the wound from contamination sources creating an efficient cover that acts as a effective defensive and protecting barrier,
- to prevent tissue mistreatment, local pain, and stress,
- to debride the devitalized tissues without interfering with living tissues, thus preventing the accumulation of secretions in the injury, reduce inflammation in the area, and prevent infections by controlling bacterial growth.

The instant invention, as recited in claim 1, is directed to a topical composition in form of a gel for treating skin burns, which contains the following components:

a first barrier gel for skin protection comprising

carboxypolymethylene as a first thickening agent, and

an emulsifier agent, wherein the carboxypolymethylene and emulsifier agent are in an aqueous carrier;

a second barrier gel for skin protection comprising

a second thickening agent, and

a preservative agent, wherein the second thickening agent and preservative agent are in an aqueous carrier;

an active principle having proteolytic activity;

chlorhexidine in a pharmaceutically effective amount; and

an anesthetic agent.

Distinctions between the instant invention and the prior art

The present invention provides unexpected improvements over the prior art by creating two protective gel barriers which are prepared separately. The first protective gel barrier is composed of carboxypolymethylene, (e.g. in an amount of 1.5 - 2.5 wt %) in an aqueous vehicle with an emulsifier (e.g. triethanolamine). Carboxypolymethylene is a high-molecular weight

synthetic resin (i.e. polymer matrix), which is polymerized with a hydrophobic monomer, thus obtaining an acrylic or polyacrylic acid polymer.

The carboxypolymethylene maintains the homogeneity of the preparations by stabilizing emulsified systems against sedimentation or separation, and by absorbing the respective interface. The carboxypolymethylene also is a thickener that increases the viscosity of solutions.

The present invention has the unexpected advantages of efficiently forming the protecting barrier, cleaning undesired oily substances, evenly distributing the preparation over the skin and accelerating the stabilization of the protective gel barrier. The composition of the invention is further translucent, does not cause skin irritation and is non-toxic. It further coalesces rapidly the application of the product, giving it consistency.

The second protective gel barrier of the instant invention, is composed of thickening agent, such as carboxymethylcellulose (CMC) (in, e.g. an amount of 1 - 4 wt %), and a preservative (e.g. parabene) in an aqueous vehicle. Sodium CMC is the sodium salt of a cellulose polycarboxymethyl ether, a high viscosity water-soluble anionic polymer. The CMC in the composition functions as a high quality thickener, which is compatible with other colloids, electrolytes, alcohols, etc. In addition, the CMC is easily dissolved in cold or warm water and is a dispersion suspending stabilizing agent. Further the CMC retains water contributing to the dryness of the underlying injury and acts as a film-generating agent resistant to oils, greases, and organic solvents. It also acts as a binding agent and protective colloid.

The CMC also acts as a rheologic agent, i.e., it regulates flow properties, and has binding, emulsifying, dispersing, and agglutinant properties. It does not coagulate with heating below 40°C. CMC shows resistance to microbiological attacks, stability within a pH range of 4 to 9, being ideal at neutral pH, and is physiologically inert, an essential property for the desired effect.

The mixture of the two protective gel barriers constructs a topical gel composition having unexpected advantageous properties for the treatment of superficial burns and skin injuries.

The composition of the invention utilizes a proteolytic enzyme because of its exclusive dead tissue debridating action that respects healthy ones, an ideal action for the treatment of skin injuries.

The composition of the invention also uses an anesthetic for the immediate or mediate application of the composition, thus avoiding pain and stress, namely, one of current priorities in the treatment of superficial skin injuries or burns.

The composition of the invention also uses chlorohexidine as an antiseptic because of its bactericidal, bacteriostatic, and non-toxic properties. Chlorhexidine is free of bacterial resistance, active against skin bacteria, can be used in an aqueous solution, is non-irritant, with persistent antibacterial activity on the skin; as well as being quick acting, with minimum absorption, and does not delay wound healing.

The composition of the invention creates a protective gel shell (through the combination of the first and second barrier gels) combined with the debridating effects of the proteolytic enzyme, the antibacterial properties, and the comfort and analgesia provided by the anesthetic.

The composition may be applied immediately or mediately and proves beneficial in superficial skin injuries at the beginning of the tissue regeneration process for abrasions, superficial burns, chemical burns, avulsions, viral skin injuries, non-secreting infectious skin injuries, surgical wounds, dermal abrasions, and as an adjuvant in the treatment of deeper injuries.

The present inventive composition is both novel and unobvious over the prior art and presents a composition having the advantages of:

- promoting ideal conditions for the regeneration of skin epithelia.
- removing both debris and necrotic tissues.
- preventing tissue mistreatment because it does not adhere to the injury
- suppressing pain and stress to the patient, thus preventing autonomic, somatic, and endocrine responses.
- suppressing local pain at the injury though two mechanisms: i.e. by covering nerve endings, and though an analgesic action
- creating a protective defense barrier for the body, thus isolating injuries from contamination sources
- preventing the accumulation of secretions in the injury
- preventing wound dehydration due to water evaporation
- removing bacteria by virtue of its antiseptic component

- promoting rapid epithelialization, thus decreasing the formation of scars.

Klein - Klein teaches a topical composition for the treatment of burns, injuries, and scars, wherein the active ingredient is a cereal-derived (1-3) (1-4) ß-D-glycan. More particularly, the composition of Klein is related to topical cream and gel formulations with cleansing, hydrating, softening, and anti-pruriginous activities for the topical treatment of burns, wounds, and other skin injuries and conditions.

Klein uses carboxypolymethylene as a vehicle without any specific therapeutic function. In the description of the reference of gels it is used at 0.5%, whereas the instant composition of claim 5 uses it at 1.5% - 2.5% with a therapeutic action.

The components in Klein are all mixed to create creams and gels, whereas with the present invention two barrier gels are required, which each have different required components. In addition, with the Klein composition both triethanolamine and parabenes are used as stabilizers and preparation preservatives.

Klein fails teach or suggest a composition having the advantages that are associated with the present invention as dicussed above. Specifically, Klein fails to teach or suggest a composition that provides ideal conditions for skin epithelium regeneration; removes both debris and necrotic tissues; suppresses pain and thus prevents stress to the patient, which in turn prevents autonomic, somatic, and endocrine responses. Klein neither teaches nor suggests a composition that suppresses local pain in the injury by 1) covering nerve endings and 2) analgesic action. Nor does Klein teach or suggest the creation of a protecting defense barrier for the body, isolating the injury from contamination sources, preventing the accumulation of secretions in the injury, removing bacteria by virtue of an antiseptic component or creating a rapid epithelialization process, thus decreasing scar formation.

Thus, there is no disclosure or suggestion in Klein regarding a composition composed of two barrier gels nor of the advantages associated therewith.

Parrilla - Parrilla fails to make up for the deficiencies of Klein. Parrilla discloses a composition for the treatment of skin injuries, such as burns. The composition of Parrilla is a film used to

isolate and protect injuries and includes an antiseptic (benzalkonium chloride), a sapogenin (filiferin), and a proteolytic enzyme (papain), in a suitable hydrophilic colloid vehicle based on carboxymethylcellulose.

The composition of Parrilla prevents external stimulation because it is in contact with the nerve endings of the injury, thus suppressing pain. The physical barrier prevents the passage of microorganisms that may contaminate the wound. The antiseptic cleans the wound of any existing microorganisms. It reinforces proteolysis and accelerates the biochemical debridement processes.

However, as discussed above, the composition of the invention requires two protective barrier gels that together form a composition that create an isolating shell, i.e. a protecting defense barrier for the body. The first barrier gel of the invention maintains the homogeneity of the preparations, stabilizes the emulsified system, absorbs the respective interface, helps efficiently form the protecting barrier, cleans undesired oily substances, distributes evenly the preparation over the skin, accelerates the stabilization of the protective gel barrier, is translucent, does not cause skin irritation, is non-toxic, and coalesces very quickly upon the application of the product, thus giving it consistency. The second barrier gel is a thickener, compatible with other colloids, electrolytes, alcohols etc, and also a dispersion stabilizer, and a water retaining agent that contributes to the dryness of the underlying injury. It acts as a film-generating agent which is resistant to oils, greases, and organic solvents; it also acts as a binder and is a protective colloid, which acts as rheologic agent, i.e. regulates flow properties, and is resistant to microbiological attacks.

The composition of the invention provides analgesia not only by covering nerve endings but also with the use of a local anesthetic, such as lidocaine; thus, suppressing pain produced by chemical substances from inflammation and ischemia (histamine, serotonin, etc.), which is described as nociceptive pain and which causes autonomic, somatic, and endocrine responses.

The composition of the invention not only succeeds in preventing the passages of contaminating microorganisms through protective barrier gels, but also provides improved antiseptic and anti-infective advantages. Benzalkonium chloride, which is used in Parrilla, is only moderately efficient as an antiseptic, and it is removed very quickly from surfaces and

becomes contaminated very rapidly. In addition, toxicity has been described with benzalkonium in aquatic environments.

On the other hand, chlorhexidine, the specific antiseptic of the presently claimed composition, has important advantages, such as being an efficient bactericidal and/or bacteriostatic agent, non-toxic, free of bacterial resistance, active against skin bacteria, useful in aqueous solution, non-irritant, with persistent antibacterial activity on the skin, and a rapid onset of action, minimum absorption and chlorhexidine does not delay wound healing.

Parrilla's composition shows the therapeutic value of proteolytic enzymes in superficial non-infected skin injuries. The prior art composition accelerates the debridement process, thus making the environment less apt for bacterial colonization through removing debris and shortening epithelialization time. Thus, Parrilla teaches the use of a proteolytic enzyme for tissue debridement to prevent the occurrence of infections, but it is not indicated to treat infection once it occurs and and is not specific to remove bacteria.

Parrilla fails to teach or suggest a composition having two barrier gels that allows for the formation of an isolating shell, i.e. a protecting defense barrier for the body. Parrilla similarly fails to teach the advantages of the invention of a composition that suppresses inflammatory nociceptive pain, prevents stress to the patient and his/her tissues, and thus avoids autonomic, somatic, and endocrine responses; suppresses local pain in the injury by the mechanism of analgesic action of an anesthetic agent; removes bacteria and disinfects the wound through the use of a highly bactericidal and bacteriostatic non-toxic antiseptic component. Thus, as note above, Parrilla fails to teach the deficiencies that are found in Klein.

Beitner - Beitner similarly fails to make up for the deficiencies of Klein and/or Parrilla so as to teach or suggest the instant invention. Beitner teaches the topical use of psychiatric drugs, such as thioridazine, as analgesics for burns, sun burns, and freezing injuries by interfering with the action of the "calcium-calmodulin complex." Beitner mentions the topical anesthetic agent lidocaine hydrochloride in an amount of 0.1 - 10 wt% as an adjuvant in the study. However, Beitner neither teaches nor suggests a composition having two barrier gels that provides ideal conditions for skin epithelium regeneration; helps to remove debris and necrotic tissues; prevents tissue mistreatment during intervention by not adhering to the injury; suppresses local pain in the

injury by creating a cover over nerve endings; creates a protecting defense barrier for the body by isolating the injury from contamination sources; prevents the accumulation of secretions in the injury; prevents wound dehydration due to water evaporation; removes bacteria by virtue of its antiseptic component; and creates a rapid epithelialization process, thus decreasing scar formation.

Thus, the instant invention cannot be achieved or suggest by the combined teachings of Klein, Parrilla and Beitner. Withdrawal of the rejection is respectfully requested.

Chen – Chen fails to teach or suggest the features of the invention that are omitted from Klein, Parrilla and Beitner. Chen teaches a topical spray for the treatment of burns that incorporates chlorhexidine in an amount of 0.05 - 10 wt%. Chen describes chlorhexidine as an antiseptic and disinfecting agent effective against a wide range of bacteria, certain fungi, and certain viruses. Chen mentions preparations with the anti-infectious properties owing to chlorhexidine.

However, Chen similarly fails to teach a composition having two barrier gels that provides ideal conditions for skin epithelium regeneration; promotes the elimination of debris and necrotic tissues; prevents tissue mistreatment during interventions by not adhering to the injury; prevents stress to the patient and his/her tissues by suppressing pain and, thus prevents autonomic, somatic, and endocrine responses; suppresses local pain of the injury through two mechanisms: covering nerve endings and analgesic action; creates a protecting defense barrier for the body, thus isolating the injury from contamination sources; prevents the accumulation of secretions in the injury; prevents wound dehydration due to water evaporation and creates a rapid epithelialization process, thus decreasing scar formation. Thus, the instant invention is neither taught nor suggested by the combined references of Klein, Parrilla, Beitner and Chen and withdrawal of the rejection is respectfully requested.

In view of the above amendment, Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD, Registration No. 40069 at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

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Respectfully submitted,

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